(b) binding the selected drugs to the selected synthetic receptors to produce a multi-prodrug complex; and

(c) administering the multi-prodrug complex to an organism so that the selected drugs dissociate from the synthetic receptors and bind to the drugs' pathophysiologic receptors.

29. The method of claim 28 wherein the multi-prodrug complex is attached to a biologic or biocompatible structure.--

---

REMARKS

Claims 2, 4, 6 and 8-13 are pending in the instant application. Claims 2, 4, 6 and 8-13 have been rejected. Claims 2, 4, 6, 8, 9, 10, 11 and 12 have been canceled. Subject matter of the canceled claims is represented in new claims 14-29. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Objection under 35 U.S.C. § 132

The Examiner has objected to the amendments filed August 20, 1999 because they are suggested to introduce new matter into the disclosure. Specifically, the Examiner suggests that the proviso that the synthetic receptor is not a polypeptide derived from a naturally occurring protein to which the drug binds is not

supported by the original disclosure. Accordingly, in an earnest effort to advance the prosecution of this case, Applicant has canceled all claims containing this proviso. New claims drawn to subject matter of the canceled claims do not contain this proviso. Withdrawal of this objection is therefore respectfully requested.

II. Rejection of Claims 2, 4, 6 and 8-13 under 35 U.S.C. § 112, first paragraph

Claims 2, 4, 6 and 8-13 have been rejected under 35 U.S.C. § 112, first paragraph, as the Examiner suggests that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The Examiner has acknowledged that the specification is enabling for a synthetic receptor and drug that binds to the synthetic receptor. However, the Examiner suggests that the specification does not reasonably provide enablement for the proviso that the synthetic receptor is not a polypeptide derived from a naturally occurring protein to which the drug binds.

At the outset, it is respectfully pointed out that claim 13 does not contain this proviso. Further, claim 13 does not depend from any claims containing this proviso. Accordingly, inclusion of claim 13 within this rejection is improper.

With respect to rejected claims 2, 4, 6, and 8-12, in an earnest effort to advance the prosecution of this case, Applicant has canceled these claims, representing the subject matter in new claims 14-29. New claims 14-29 do not contain this proviso but rather specifically state methods by which the synthetic receptor is selected (see new claims 14-21) or the group of molecules from which the synthetic receptor can be selected (see new claims 22-29). Support for new claims 14-21 can be found throughout the specification and in particular at page 9, line 28, through page 10, line 11. Support for new claims 22-29 can be found throughout the specification and in particular at page 8, lines 2-28, page 10, lines 11-16 and page 12, lines 10-18.

Withdrawal of this rejection is respectfully requested in light of these remarks and amendments to the claims.

III. Rejection of Claims 2, 4, 6 and 8-13 under 35 U.S.C. § 103(a)

Claims 2, 4, 6 and 8-13 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Morgan, Jr. et al. The Examiner suggests that it would have been obvious to one skilled in the art at the time the invention was made to deliver a drug via a prodrug complex where the drug is bound to a polymeric carrier such that the drug would dissociate during *in vivo* administration, but would maintain its activity by preferentially binding to its pathologic

receptor over the polymeric carrier with the expected result of reducing the drug's toxicity. Applicant respectfully traverses this rejection.

At the outset, Applicant respectfully disagrees with the Examiner's suggestion that the statement in the '713 patent at column 2, lines 61-63, "Drug activity also is preserved *in vivo* after administration of the conjugate to a human or mammalian host", teaches that the drug's affinity for the polymeric receptor is less than that for its pathophysiologic receptor. Nowhere in the '713 patent is the drug's pathophysiologic receptor even discussed. Nor is there any mention in this patent of a drug's affinity for the polymeric carrier as compared to its pathophysiologic receptor.

Teachings in the '713 patent regarding affinity of a drug relate only to achieving high affinity or tight binding with the polymeric carrier. See, for example, column 6, lines 56-60, where it is taught that the smallest peptide fragment capable of noncovalent binding is used, unless it has a low affinity drug-binding domain, in which case a larger fragment may be advisable. Also see column 11, lines 18-20 where modifications for achieving tighter drug binding are described and column 14, lines 57-58 where a preference for tight binding is described.

However, no guidance whatsoever is provided in the '713 patent with respect to the drug's affinity for the polymeric carrier being less than that for its pathophysiologic receptor. In fact, the statement cited by the Examiner at column 2, lines 61-63, when read in context, actually relates to the fact that the drug has not been covalently modified. See specifically column 2, lines 5-15 where the prior art problem of covalent conjugation of drugs to carrier molecules (which is solved by the polymeric carriers of the '713 invention) is taught. At column 2, lines 12-15, it is stated that "The drug modification often results in the loss of some of the activity of the drug molecule due to chemical modification of some of the functional groups within the drug molecule." At column 2, lines 16-18, it is taught that "exposure to derivatization conditions may completely inactivate the drug." Then, at column 2, lines 23-26, it is taught that there is a "need in the field of drug conjugation to be able to attach multiple drug molecules to the targeting antibody without covalent modification of the drug and loss of activity." Finally, in the sentences directly preceding that relied upon by the Examiner, at column 2, lines 55-61, it is taught that "A method for preserving the therapeutic activity is disclosed . . . comprising noncovalently binding the drug to a polymeric carrier. The drug activity is thus preserved

during subsequent chemical reactions, such as the reactions used to attach the polymeric carrier to a targeting protein to form a conjugate." The next sentence, "Drug activity also is preserved in vivo after administration of the conjugate to a human or mammalian host" thus clearly relates to noncovalent attachment of the drug to the polymeric carrier not modifying drug activity.

In contrast to the invention of the '713 patent, the instant invention does not turn on drug delivery methods that avoid covalent drug modification. See page 9, lines 15-27, of the instant specification where it is taught that drugs and synthetic receptors may be attached either covalently or noncovalently to a biologic or biocompatible structure and that the drugs may be chemically modified for attachment. Instead, as also taught at page 9, the instant invention relies upon affinity-based partitioning of drugs between synthetic receptors and pathophysiologic receptors.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must

teach or suggest all the claim limitations. See MPEP § 2142. Further, MPEP § 2142 and the case law require that the teaching or suggestion to make the claimed combination and the reasonable expectation of success both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The '713 patent does not meet these criteria with respect to the instant invention.

In an earnest effort to advance the prosecution, Applicant has canceled pending claims 2, 4, 6 and 8-12. Subject matter of these claims is represented in new claims 14-29 which further clarify distinctions between the instant invention and the polymeric carriers taught by the '713 patent. For example, new claims 14-29 clearly state that the selected drugs of the prodrug and multi-prodrug complexes of the present invention bind to the synthetic receptors with lower affinity than to the drugs' pathophysiologic receptors so that the selected drugs dissociate from the synthetic receptors and preferentially bind to the pathophysiologic receptors. Support for this statement can be found throughout the specification including claims 11 and 12, now canceled, and in particular at page 9, lines 1-6 where it is taught that the complexes of the present invention rely upon drug partitioning through differential affinity for a synthetic receptor versus the

targeted pathophysiologic receptor. Nowhere does the '713 patent teach or suggest prodrug complexes or multi-prodrug complexes with this limitation.

In addition, new claims 14 and 21 specify methods, taught in the specification at page 9, line 28, through page 10, line 11, by which the synthetic receptor is selected. None of these selection methods are taught nor suggested by the '713 patent. New claims 22-29 list specific synthetic receptors taught in the specification at pages 8, 10 and 12, for use in the prodrug complexes of the present invention. None of the specified synthetic receptors of claims 22-29 fit the definition of polymeric carriers of the '713 patent.

The '713 patent does not teach or suggest prodrug or multi-prodrug complexes with the limitations as set forth in new claims 14-29.

With respect to pending claim 13, there is no teaching or suggestion in the '713 patent of immobilization of their polymeric carrier complex. Thus, the cited reference fails to teach or suggest all the limitations of the claimed invention.

Accordingly, this reference fails to meet the basic criteria for a *prima facie* obviousness rejection of either claim 13 or new

claims 14-29. Withdrawal of this rejection is therefore respectfully requested.

IV. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Kathleen A. Tyrrell
Registration No. 38,350

Date: **January 13, 2000**

Law Offices of
JANE MASSEY LICATA
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515